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EDITORIALS

Is It Worth Correcting Hyperparathyroidism if Hyperphosphatemia and Hypocalcemia Worsen? A Cinacalcet Story

Related Article, p. 197

Mineral and bone disorders (MBD) are common and are associated with adverse outcomes in chronic kidney disease (CKD).^{1,2} The 2 fundamental questions are whether there are effective interventions to correct CKD-MBD and, if so, whether such interventions improve outcomes. Treatment modalities for CKD-MBD range from nutritional interventions to various pharmaceutical agents. The aims of therapy are to correct hyperparathyroidism and to control serum phosphorus and calcium levels. In this issue of the *American Journal of Kidney Diseases*, Chonchol and colleagues report the results of a phase 3 trial of cinacalcet for treatment of hyperparathyroidism in CKD patients.³ In this editorial, we review the implications of cinacalcet therapy on serum phosphorus and calcium across the range of CKD stages.

Cinacalcet activates the calcium sensing receptor (CaSR) indirectly by enhancing its sensitivity to extracellular calcium.⁴ As a result, even a low serum calcium level can suppress CaSR-dependent parathyroid hormone (PTH) secretion, making cinacalcet an effective agent for correcting secondary hyperparathyroidism.⁵ The consequences of cinacalcet therapy are reminiscent of the effects of parathyroid resection.⁶ In dialysis patients, cinacalcet-induced "medical parathyroidectomy"^{6,7} lowers serum calcium and phosphorus concentrations, similar to what is observed in "hungry bone syndrome."⁸ The decline in serum phosphorus level is probably the result of both decreased phosphorus release from (or its increased uptake to) the bone and its decreased

intestinal absorption.⁹ This bonus effect of cinacalcet is in sharp contradistinction to the worsening of hyperphosphatemia often observed with vitamin D sterols, as vitamin D sterols suppress PTH secretion by stimulating vitamin D receptors (VDR) of the parathyroid glands, but also stimulate VDRs of the intestinal tract, leading to enhanced phosphorus absorption (Table 1).¹⁰ Another unique effect of cinacalcet is a reduction in serum calcium concentration, probably as a result of reduced bone turnover activity (as manifested by a decline in serum alkaline phosphatase),¹⁴ increased urinary calcium excretion,^{15,16} and, possibly, decreased intestinal calcium absorption. This hypocalcemic effect of cinacalcet is also in contrast to the hypercalcemic effects of vitamin D sterols (Table 1).¹⁷

In contrast to what is seen with kidney failure, in patients with earlier stages of CKD, cinacalcet-induced PTH suppression mitigates the phosphaturic effect of PTH, leading to decreased urinary phosphorus excretion and increased phosphorus retention in the body.¹⁸ Cinacalcet-associated hyperphosphatemia was first observed in the phase 2 trial by Charytan et al,¹⁸ in which the cinacalcet arm exhibited significantly higher occurrence of serum phosphorus levels greater than 4.7 mg/dL after 4 weeks of therapy. Similarly, in

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Table 1. Comparison of Changes in Relevant Serum and Urine Measurements Upon Administration of Cinacalcet Versus Activated Vitamin D Analogs

	Cinacalcet		Vitamin D Analogs*	
	CKD 3-4	CKD-5D	CKD 3-4	CKD-5D
Serum calcium	↓	↓	↑	↑
Serum phosphorus	↑	↓	↑↔†	↑
Serum PTH	↓	↓	↓	↓
Serum FGF-23	↓↔ (?)‡	↓↔ (?)‡	↑	↑
Serum calcitriol	↓ (?)	↓ (?)	↑↓ §	↑↓ §
Serum alkaline phosphatase	↓ (?)	↓	↓	↓
Urine calcium	↑	NA	↑↔†	NA
Urine phosphorus	↓	NA	↑↔†	NA

Note: CKD stages 3 and 4 also include kidney transplant recipients. CKD-5D includes long-term dialysis patients.

Abbreviations: CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; NA, not applicable; PTH, parathyroid hormone.

*Magnitude of the effect may vary according to product used.

†A recent randomized controlled trial showed no increase in serum phosphorus, nor any changes in urine calcium or phosphorus in patients treated with paricalcitol.¹¹

‡Some preliminary data from kidney transplant recipients have indicated a decline in FGF-23 upon cinacalcet treatment.¹²

§Native serum calcitriol levels may decrease with the administration of paricalcitol.¹³

another unpublished phase 2 trial, use of cinacalcet in persons with CKD stages 3 and 4 led to an increase in serum phosphorus from 4.1 mg/dL at baseline to 4.9 mg/dL at 16 weeks, and 30% of these patients had to either initiate de novo treatment with phosphorus binders or increase their binder dose.^{19,20} The hyperphosphatemic effect of cinacalcet has also been confirmed in kidney transplant recipients.^{16,21} Vitamin D sterols may also lead to hyperphosphatemia, but this effect is somewhat consistent across the entire range of CKD,¹¹ and the antiphosphaturic effect of PTH suppression with vitamin D sterols in non-dialysis-dependent CKD is practically neutralized by the phosphaturic effect of elevated fibroblast growth factor (FGF) 23 induced by vitamin D receptor activation (Table 1).^{22,23} Accordingly, in a recent clinical trial in patients with CKD stages 3 and 4, urinary phosphorus excretion was similar in patients who received oral paricalcitol and those in the placebo group.¹¹ In contrast, cinacalcet probably has either no effect on FGF-23 (Eduardo Slatopolsky, personal communication) or, as recently shown in kidney transplant recipients, decreases FGF-23,¹² leading to a decline in urinary phosphorus excretion and resultant hyperphosphatemia.

In the study by Chonchol and colleagues, a 32-week phase 3 double-blind, randomized controlled trial of 404 individuals with CKD stages 3 and 4 and with random 3:1 assignment to cinacalcet

versus placebo,³ cinacalcet administration corrected hyperparathyroidism; however, it also led to a 21% rise in serum phosphorus, as compared to a 6% rise among controls (4.5 ± 1.0 mg/dL v 4.0 ± 0.7 mg/dL, respectively).³ Another less favorable outcome was hypocalcemia, as 62% of cinacalcet-receiving participants had at least 2 consecutive serum calcium concentrations below 8.4 mg/dL despite concurrent vitamin D therapy, compared with only 1% in the placebo group. At 32 weeks, serum calcium was 1.0 mg/dL lower in the cinacalcet group versus the placebo group (8.9 ± 0.8 mg/dL v 9.9 ± 0.6 mg/dL). The result of the concurrent hyperphosphatemia and hypocalcemia was an unchanged calcium-phosphorus product.³

The phase 2 (Charytan et al¹⁸) and 3 (Chonchol et al³) cinacalcet studies in CKD stages 3 and 4 raise the question of whether a reduction in PTH at the expense of worsening hyperphosphatemia and hypocalcemia is in the best interest of the patient. First, what is the benefit of reducing PTH? A recent observational study suggested that secondary hyperparathyroidism was associated with higher mortality in 515 male US veterans with moderate to severe CKD.²⁴ The association of high PTH and increased death risk appeared to be independent of serum levels of calcium or phosphorus.²⁴ However, in several observational studies in long-term dialysis patients, both low and high PTH levels appeared to

Table 2. Overview of Randomized Controlled Trials of Cinacalcet in Nontransplanted CKD Patients

Reference	Study Population	Drug Dose/Control	Results	Comments
Lindberg et al, ⁴⁴ 2005	N = 395; Patients with SHPT on HD or PD	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Significant reduction of PTH, Ca, P, and Ca × P with cinacalcet	Randomized, placebo-controlled, double-blind study
Block et al, ⁴⁵ 2004	N = 741; Patients with SHPT on HD	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Significant reduction of PTH and Ca × P with cinacalcet	Randomized, placebo-controlled, double-blind studies; data from 2 trials combined
Moe et al, ⁴⁶ 2005	N = 1,136; Patients with SHPT on HD or PD	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Significantly higher likelihood to achieve KDOQI bone-mineral targets with cinacalcet	Randomized, placebo-controlled, double-blind studies; data from 3 trials combined
Schaefer et al, ⁴⁷ 2008 (SENSOR)	N = 673; Patients with uncontrolled SHPT on HD	Cinacalcet with post-dialysis meal + standard SHPT therapy v cinacalcet with food during dialysis + standard SHPT therapy	Noninferiority of post-dialysis-administered cinacalcet	Randomized, active comparator-controlled, open label study
Malluche et al, ⁴² 2008	N = 48; Patients with uncontrolled SHPT on HD	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Reduced bone turnover and tissue fibrosis after cinacalcet therapy	Randomized, placebo-controlled, double-blind study
Messa et al, ³⁰ 2008 (OPTIMA)	N = 552; Patients with uncontrolled SHPT on HD	Cinacalcet + standard SHPT therapy v standard SHPT therapy	More patients in the cinacalcet arm achieved KDOQI bone-mineral treatment targets	Randomized, open label study
Fukagawa et al, ⁹ 2008	N = 144; Japanese patients with uncontrolled SHPT on HD	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Significant reduction of PTH with cinacalcet	Randomized, placebo-controlled, double-blind study in Japan
Sterrett et al, ⁴⁸ 2007	N = 266; Patients with uncontrolled SHPT on HD	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Sustained reduction of PTH, Ca, P, and Ca × P with cinacalcet	Double-blind 12-month extension study
Charytan et al, ¹⁸ 2005	N = 54; Patients with eGFR 15-50 mL/min/1.73 m ² and PTH > 130 pg/mL	Cinacalcet + standard SHPT therapy v placebo + standard SHPT therapy	Significant reduction in PTH with cinacalcet	Randomized, placebo-controlled, double-blind study
Chonchol et al, ³ 2009	N = 404; Patients with eGFR 15-59 mL/min/1.73 m ² and PTH > 100 (CKD stage 3) or > 160 (CKD stage 4) pg/mL	Cinacalcet v placebo	Significant PTH reduction and increased incidence of serum calcium < 8.4 mg/dL for cinacalcet compared with placebo	Randomized, placebo-controlled, double-blind study; extension study halted by sponsor due to safety concerns

Note: Conversion factors for units: serum calcium in mg/dL to mmol/L, $\times 0.2495$; eGFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$. Parathyroid hormone levels expressed in pg/mL and ng/L are equivalent.

Abbreviations: Ca, calcium; Ca × P, calcium-phosphorus product; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; OPTIMA, An Open-label, Randomized Study Using Cinacalcet to Improve Achievement of KDOQI Targets in Patients With ESRD; P, phosphorus; PD, peritoneal dialysis; PTH, parathyroid hormone; SENSOR, Study to Investigate Cinacalcet Treatment in Haemodialysis Patients With Secondary Hyperparathyroidism; SHPT, secondary hyperparathyroidism.

be associated with increased mortality compared with PTH in the 100 to 300 pg/mL range.^{25,26} These U-shaped associations are usually interpreted as unfavorable outcomes related to both high-turnover and adynamic bone disease.^{26,27} Nevertheless, when PTH is below 100 pg/mL, vitamin D analogs and/or cinacalcet are usually withheld due to the “adynamic bone disease apprehension,”²⁷ hence eliminating the hypothesized survival benefits of vitamin D analogs^{26,28} or cinacalcet²⁹ in low PTH ranges.

Second, what is the consequence of inducing hypocalcemia? Indeed, in several trials, a notable increase in the use of calcium-based phosphorus binders has been observed in the cinacalcet arm, probably reflecting the effort to compensate for the calcium-lowering effect of cinacalcet.³⁰ Whereas hypercalcemia appears associated with increased mortality according to most observational studies,²⁵ the adverse effects of acute or chronic hypocalcemia in CKD patients are less well described. Two recent large epidemiologic studies in long-term hemodialysis patients showed that more than a moderate drop in serum calcium may be associated with increased mortality.^{25,31} A drop in serum calcium greater than 0.6 mg/dL over 6 months was associated with an approximately 40% increase in death risk.²⁵ Since both acute and chronic hypocalcemia may be proarrhythmogenic and associated with cardiovascular and musculoskeletal abnormalities,^{32,33} it may be prudent to avoid extreme declines in serum calcium or levels below 8.4 mg/dL.³⁴

Third, what is the consequence of raising serum phosphorus? It may be argued that the concurrent hypocalcemia would offset the deleterious effect of hyperphosphatemia by maintaining the calcium-phosphorus product essentially unchanged. Indeed, in the current study, the end-trial calcium-phosphorus product was $40.1 \pm 8.3 \text{ mg}^2/\text{dL}^2$ in the cinacalcet group versus $38.9 \pm 6.9 \text{ mg}^2/\text{dL}^2$ among controls.³ However, the biological plausibility and clinical utility of the calcium-phosphorus product in the management of CKD-MBD has been questioned.³⁵ It is also not clear whether a higher calcium-phosphorus product is a risk factor for vascular calcification, since in most observational studies there has been no association or only a weak association between this parameter and vascular calcification.³⁵⁻³⁸ Higher se-

rum phosphorus has been associated with increased mortality in CKD patients independent of serum calcium levels.³⁹

Additional unanswered questions remain about the effects of cinacalcet on plasma calcitriol, FGF-23, and alkaline phosphatase levels. Cinacalcet might worsen calcitriol deficiency by sensitizing CaSR in the proximal tubule and reducing circulating PTH levels, both of which can suppress 1α -hydroxylation of 25-hydroxyvitamin D.^{40,41} The latter effect can be opposed by concurrent administration of vitamin D or its analogs. Indeed, in the current phase 3 study, not only were cholecalciferol and ergocalciferol offered to participants in the cinacalcet arm, but calcitriol intake was also encouraged to prevent very low calcium levels.³ Even though the impact of cinacalcet on FGF-23 levels is currently only speculative (see previous discussion), cinacalcet can reduce serum alkaline phosphatase concentrations at least in long-term dialysis patients (Table 1),¹⁴ probably by correcting high-turnover bone disease.⁴² This can be seen as another salutary effect of cinacalcet, especially since increased alkaline phosphatase levels are associated with increased mortality.⁴³

In summary, the current phase 3 cinacalcet trial³ in patients with CKD stages 3 to 4 confirms the findings that were reported earlier in the phase 2 study.¹⁸ What stands out as the main difference between these patients and those with kidney failure treated by dialysis is the rise in serum phosphorus in the former group,^{3,18} contrasting with the robust phosphorus-lowering effect that has been repeatedly described in several clinical trials of dialysis patients (Table 2). In long-term dialysis patients, cinacalcet therapy can engender conditions similar to parathyroidectomy and hungry bone syndrome with resultant hypocalcemia and hypophosphatemia, whereas in patients with CKD stages 3 to 4 it creates the clinical picture of primary hypoparathyroidism with concurrent hyperphosphatemia and hypocalcemia.⁴⁹ In our opinion, the hyperphosphatemic and hypocalcemic effects of cinacalcet in CKD stages 3 to 4 mitigate the level of enthusiasm for its use. Hyperphosphatemia and hypocalcemia have similarly been reported in several small cinacalcet studies in kidney transplant recipients,^{16,21,50} but cinacalcet can be an appropriate treatment in these patients, especially when re-

fractory (tertiary) hyperparathyroidism and its associated hypercalcemia and hypophosphatemia persist posttransplantation.⁵⁰ The intense marketing battle among pharmaceutical companies manufacturing CKD-MBD medications has led to a highly polarized environment that may confound appropriate judgment about the scientific and public health merits of therapeutic interventions.⁵¹ Notwithstanding that our opinions may be confounded by such biases, we tend to conclude that in nontransplant CKD stages 3 and 4, the indication for cinacalcet therapy appears somewhat limited at this time, and its use as an adjunct therapy needs further investigation.

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